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De Novo Interstitial Tandem Duplication of Chromosome 4(q21–q28)

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We describe a girl with a previously unreported de novo duplication of chromosome 4q involving segment q21–q28. Clinical manifestations included growth and psychomotor retardation, facial asymmetry, hypotelorism, epicanthic folds, mongoloid slant of palpebral fissures, apparently low-set auricles, high nasal bridge, long philtrum, small mouth, short neck, low-set thumbs, and bilateral club foot. This phenotype is compared with that of previously reported cases of duplication 4q. © 1996 Wiley-Liss, Inc.

KEY WORDS: direct duplication 4q, tandem duplication 4q, interstitial duplication 4q, growth retardation, psychomotor retardation, minor facial anomalies

INTRODUCTION

Partial duplication of the long arm of chromosome 4 usually is the result of familial balanced translocations [Andrle et al., 1979; Biederman and Bowen, 1976; Červenka et al., 1976]. We describe a girl with a de novo interstitial tandem duplication of 4q involving the segment q21–q28.

CLINICAL REPORT

The proposita was born to a 30-year-old gravida 3, para 2, ab 1, healthy mother, and a 31-year-old father. The first pregnancy ended in a spontaneous abortion and the next one resulted in the birth of a normal boy. There was no parental consanguinity. Gestational diabetes was detected during the last 2 months of the present pregnancy and treated with insulin.

The patient was born at 37 weeks with the following measurements: weight 2,500 g (<3rd centile), length 47 cm (<3rd centile), and head circumference (OFC) 33 cm (10th centile).

At 12 months, she was hospitalized for a generalized convulsion. Physical examination showed the following: weight of 7,800 g (3rd centile), length of 70 cm (10th centile), OFC of 43.5 cm (3rd centile), facial asymmetry, mongoloid slant with short palpebral fissures, hypotelorism with bilateral epicanthic folds, apparently low-set and slightly enlarged auricles, high nasal bridge with upturned nose, long and pronounced philtrum and micrognathia with protruding upper lip, short neck, and low hairline, low-set thumbs, and club feet (Fig. 1).

Neurological examination showed hypotonia and a weak cry. No abnormalities were found on standard laboratory tests, ocular fundi, electroencephalography, brain CT scan and urinary tract examination. Congen-

Fig. 1. Front view of the patient.

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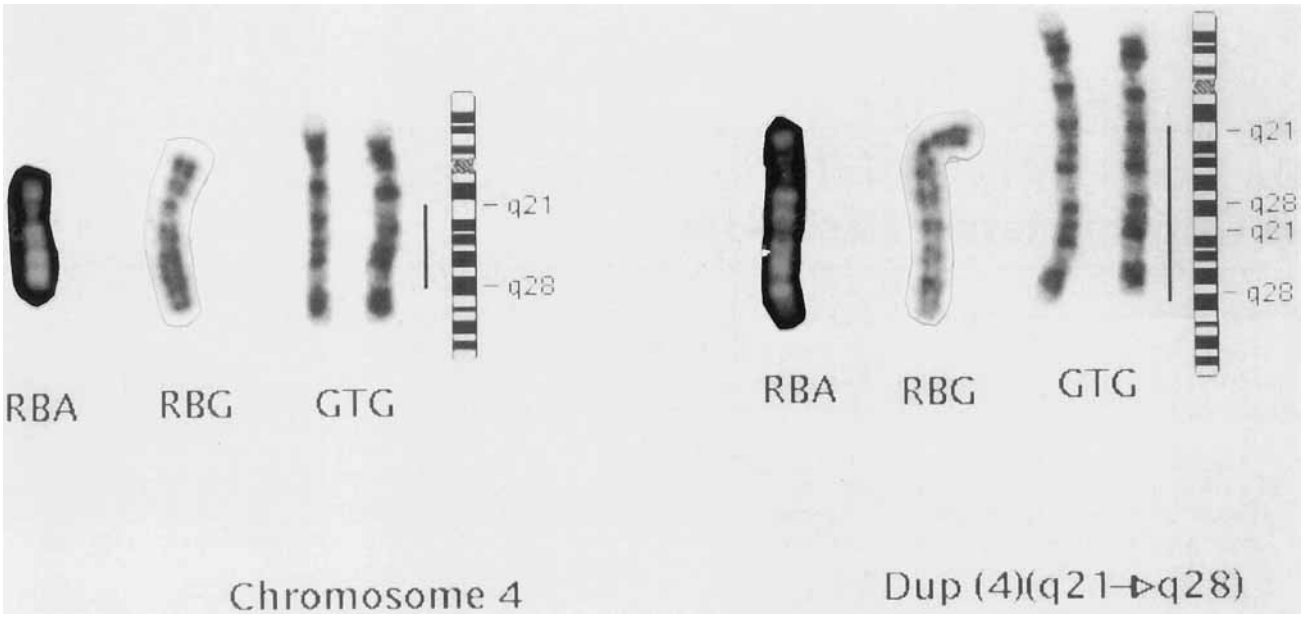

Fig. 2. Partial karyotype of the patient showing GTG, RBG, and RBA banding of chromosome 4 and dup(4)(q21–q28).

ital heart defects were absent. Psychomotor development is mildly retarded: she started laughing at 6 months, sitting at 10 months, walking alone with a wide base at 18 months. At 22 months she showed hyperactivity, had slightly increased muscle tone, and used only a few bisyllables. She has not experienced another convulsion. Her measurements were weight of 10 kg (3rd–10th centile), length of 78 cm (3rd centile), and OFC of 46.5 cm (10th centile). Hearing deficits or eye abnormalities have not been detected.

Cytogenetic studies with G and R banding techniques (Fig. 2) showed the karyotype 46,XX, dir dup(4)(q21–q28). Parents' chromosomes were normal.

Chromosome preparations were also used for fluorescence in situ hybridization (FISH) with the whole chromosome painting biotinylated probe from chromosome 4, performed according to manufacturer instructions (Oncor Inc., Gaithersburg, MD). Detection of probe hybridization was achieved by fluorescein isothiocyanate (FITC)-labelled avidin and counterstained with propidium iodide. This technique identified the extra material to be derived from chromosome 4 (Fig. 3).

DISCUSSION

During the past few years more than 30 cases of partial duplication 4q have been published involving different chromosome breakpoints [Biederman and Bowen, 1976; Červenka et al., 1976; Andrle et al., 1979; Stella et al., 1979; Fryns et al., 1980; Petit et al., 1991].

Since most of the cases are a consequence of unbalanced segregation of different reciprocal translocations, the clinical picture is quite variable depending on the duplicated segment and the concomitant monosomy. Some common findings are growth and psychomotor retardation, epicanthic folds, downward slant of palpebral fissures, large and apparently low-set ears, carp-like mouth, microcephaly, short neck, renal malformations, and heart abnormalities [Andrle et al., 1979; Červenka et al., 1976; Halal et al., 1991; Stella et al., 1979].

De novo duplications are apparently rare and might be more useful in making genotype-phenotype correlations trying to delineate a precise aneuploidy syndrome.

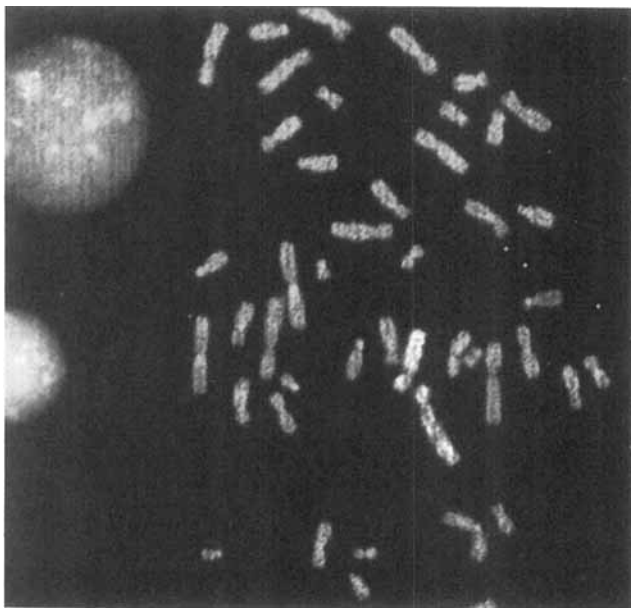

Fig. 3. Metaphase spread of patient after fluorescent in situ hybridization with chromosome 4 painting DNA probe.

TABLE I. Phenotypic Findings in Reported Patients With De Novo Duplication 4q and in the Present Case

	Vogel et al. [1975]	Taylor et al. [1977]	Dutrillaux et al. [1975]	Fryns et al. [1980]	Halal et al. [1991]	Jeziorowska et al. [1993]	Present case
Duplication 4q	q22–q34	q26–q35	q25–q34	q25–q31	q23–q27	q21.3–q31.3	q21–q28
Age (years)/sex	6/F	6½/M	2¼/F	6½/F	2¼/F	3/M	2¾/F
Growth retardation	+	+	+	+	+	+	+
Psychomotor retardation	+	+	+	+	+	+	+
Microcephaly	−	+	+	−	+	+	−
Epicanthic folds	+		+	−	+	+	+
High nasal bridge	+	+	+	+	−	+	+
Short philtrum	+	+	−	+	−	+	−
Micrognathia	+		+	−	−	+	+
"Low-set" ears	+	+	+	+	−	+	+
Thumb anomalies	+	−	+	−	−	+	+
Seizures	−	+	+	+	−	−	+
Renal hypoplasia	+		+	−	−	+	−
Congenital heart disease	−	+	−	−	+	−	−

Comparison of the phenotypic findings in our patient and all de novo previously reported patients with duplication of chromosome 4q is summarized in Table I. We do not include the case reported by Pescia et al. [1982] because the duplicated segment is more proximal and it is a mosaic with deletion 4q.

Growth and psychomotor retardation are constant in all cases. Apparently low-set ears and high nasal bridge were observed in six of seven cases. Epicanthic folds, microcephaly, micrognathia, short philtrum, and thumb anomalies are present in more than half of the cases. Facial asymmetry, described previously by Červenka et al. [1976] and Jeziorowska et al. [1993] is also present in our patient. With the few reported cases, no distinct phenotype exists with respect to duplicated segments, and more cases are needed for conclusive delineation of the duplication 4q syndrome.

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